Chapter 5

Influenza vaccine effectiveness among elderly population: evidence from an individual participant data meta-analysis

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ABSTRACT

Importance Several aggregated-data meta-analyses provided overall influenza vaccine effectiveness (VE) estimates among the community-dwelling elderly. However, these studies ignored the effect of patient-level confounders which may have biased VE estimates.

Objective To globally assess the confounder adjusted effect of influenza vaccination on laboratory-confirmed influenza among elderly population.

Data sources Potential data contributors were identified from a previously conducted aggregated-data meta-analysis addressing a similar research question.

Data extraction Twenty-nine datasets with a total of 1,829 cases and 3,146 controls were available for analysis. We conducted an individual participant data meta-analysis of test-negative design case-control studies assessing VE among elderly population. Generalized linear mixed model was used to calculate odds ratios, adjusting for age, gender, interval between symptom onset and swab collection, presence of chronic medical condition, hemisphere, and smoking status. VE was estimated as (1 – adjusted odds ratio) × 100%. Pooled VE estimates were reported according to vaccine match and intensity of the virus activity (epidemic/non-epidemic). VE was also assessed against influenza virus (sub)types H1N1, H1N1pdm09, H3N2 and B as secondary outcomes. Subgroup analyses was performed to estimate VE across several groups of elderly people.

Exposure Seasonal influenza vaccination

Main outcomes and measures Laboratory-confirmed influenza, confirmed by: culture testing, rapid antigen testing, fluorescent antibody assays, haemagglutination inhibition test or polymerase chain reaction tests.

Data synthesis Influenza vaccination was significantly effective during epidemic seasons, irrespective of vaccine match status (matched adjusted VE: 44.38%; 95%

CI 22.63 to 60.01%, mismatched adjusted VE: 20.00%; 95% CI 3.46 to 33.68%). Seasonal influenza vaccination did not show significant effectiveness during non-epidemic seasons. Additionally, there was a substantial variation in VE across virus (sub)types with the highest VE estimate for H1N1pdm09 (VE: 53.19%; 95% CI 10.25 to 75.58%). Although no statistically significant differences between subgroups could be observed, influenza vaccine did show protective effect among elderly with cardiovascular disease, lung disease, and elderly aged ≤ 75 years.

Conclusions Among the elderly population, influenza vaccination is moderately effective against laboratory-confirmed influenza during epidemic seasons. Vaccination of elderly persons remains the main strategy to reduce influenza and its complications, but more effective influenza vaccines are urgently needed.

INTRODUCTION

The ability of current inactivated seasonal influenza vaccines in reducing the risk of influenza and influenza-related complications among the high-risk group of elderly persons, referred to as influenza vaccine effectiveness (VE), varies significantly from season to season depending on factors such as intensity of influenza virus activity, interval between the vaccination and symptom onset, vaccine match to the circulating viruses, and influenza virus (sub)types [1-4]. Importantly, individual characteristics of patients such as age and presence of chronic medical conditions (e.g. cardiovascular and respiratory diseases) could also affect VE [5-7].

In order to estimate contemporary seasonal VE and explore the variation in vaccine performance across populations, test-negative design (TND) case-control studies are regularly being conducted worldwide [8]. In this type of study design, vaccination status is compared between patients presenting with influenza-like illness (ILI) symptoms who tested positive for influenza (laboratory-confirmed cases) and patients with ILI who tested negative (controls). Compared to the conventional case-control or cohort designs, TND has been found to be less susceptible to bias that arise from differences in health care-seeking behavior between cases and controls and the use of non-specific outcome measurements, such as all-cause mortality [9].

Recently we conducted an aggregated-data meta-analysis of TND studies and found that seasonal influenza vaccine was moderately effective against laboratory-confirmed influenza among the elderly population [2]. Additionally, another aggregated-data meta-analysis of TND studies found substantial variation in VE across influenza virus (sub)types among older adults [4]. Although both meta-analyses included a large number of TND studies and considered the geographical spread of influenza virus activity (epidemic condition), vaccine match [2], and virus (sub)types [4], an important limitation was that they could not adjust for individual patient-level confounders [10,11]. Besides, VE among subgroups of elderly who might be at higher risk of influenza-related complications (e.g. age above 75 years and presence of chronic medical conditions) could not be estimated from the crude aggregated data. Since TND lacks randomization of the vaccination (typical of observational study designs), baseline characteristics of vaccinated and non-

vaccinated patients could differ systematically, which could obscure the real effects of influenza vaccination [12].

To overcome the limitations of the aggregated data meta-analysis, we conducted an individual participant data (IPD) meta-analysis to estimate overall VE while adjusting for potential confounders. Additionally, we assessed VE against influenza virus (sub)types and among different subgroups of elderly people.

METHODS

Definitions and endpoints

Laboratory-confirmed influenza in outpatients and/or inpatients was the primary outcome. Influenza infection could be confirmed by at least one of the following laboratory tests: culture testing, rapid antigen testing, fluorescent antibody assays, haemagglutination inhibition test (HAI) or polymerase chain reaction tests (PCR). Secondary outcomes were VE against laboratory-confirmed A(H1N1), A(H3N2), A(H1N1)pdm09, or B virus. Cases were patients with ILI symptoms who tested positive for at least one of the influenza virus (sub)type (A(H1N1), A(H1N1)pdm09, A(H3N2), and B virus) and controls were ILI patients who tested negative for all the above-mentioned virus (sub)types. VE was defined as the relative reduction in the risk of laboratory-confirmed influenza in vaccinated compared with unvaccinated individuals in test-negative design case-control studies [2,13].

Similar to the recently published aggregated-data meta-analysis [2], VE was estimated according to the geographical spread of influenza virus activity and vaccine match to the circulating influenza viruses. For each country information about the vaccine and virus strains, predominant virus, and geographical spread of influenza activity in each epidemic season was obtained from the WHO website [2,14]. Furthermore, the decision about vaccine match or mismatch to the circulating (predominant) virus was based on haemagglutination inhibition assays (HI) reported in the WHO worksheet for each hemisphere, country, and influenza season [14]. A vaccine was considered to be a match if at least one of the two following criteria was fulfilled: (1) all the vaccine components were antigenically

similar to the reference viruses (A subtypes (H1N1 or H1N1pdm09 and H3N2) and B lineages (Victoria or Yamagata)); (2) the vaccine strains were antigenically similar to the predominant circulating virus subtypes [14]. Vaccine was considered mismatch if "there was ≥ 8-fold difference in HI titres between the vaccine antigen and ferret-derived antibodies to the circulating strain" [15, 16].

The WHO reports on geographical spread of influenza virus(es) activity during each influenza season was used to study the effect of epidemic condition on VE variation [14]. Geographical spread "refers to the number and distribution of sites reporting influenza activity" and is categorized as: sporadic activity, defined as isolated cases of laboratory confirmed infection; local activity, defined as cases limited to one administrative unit of the country (or reporting site) only; regional outbreaks, defined as cases arising in multiple, but in less than 50% of the administrative units of the country (or reporting sites); and widespread outbreaks, defined as cases recorded in 50% or more of the administrative units of the country (or reporting sites) [17]. Influenza seasons during which influenza virus(es) had a sporadic or local activity with no outbreak were considered as "non-epidemic seasons" and influenza seasons during which influenza outbreaks occurred due to the regional or widespread virus(es) activity were considered as "epidemic seasons".

Data source, Data standardization and Covariates

The search strategy, review process, selection criteria, and included studies in the aggregated-data meta-analysis have been reported previously [2]. Studies were included in the aggregated-data meta-analysis if raw data for vaccination status and outcome in people aged 60 years and older were reported or if raw data was provided by the investigators on request. If studies reported raw data for vaccination status and outcome for more than one influenza season, each influenza season was considered as a separate dataset in the meta-analysis [2]. In total 35 studies conducted by 25 authors (some authors had more than one publication) were included in the aggregated-data meta-analysis. In the current IPD meta-analysis these 25 authors were considered as the potential data contributors. A data extraction form based on the protocol for case-control studies to measure

influenza VE in the European Union and European Economic Area Member States was prepared and supplied datasets were standardized according to the form definitions [18] (Journal Web Appendix). We requested information on age, gender, presence of chronic medical condition (cardiovascular, respiratory, renal and rheumatologic diseases, hematologic and non-hematologic cancer, immunodeficiency, dementia, stroke, cirrhosis, anemia and diabetes), interval between symptom onset and swab collection, and smoking status.

Exclusion criteria

Individuals were considered vaccinated if they had been vaccinated ≥ 14 days prior to symptom onset.

Patients were excluded if their 1) unique ID was missing, 2) vaccination status was unknown, 3) outcome status (being a laboratory-confirmed case or test negative control) was unknown, and 4) a patient had multiple observations in the same influenza season. However for two patients who had multiple episodes, only the first or influenza positive episodes was included in the analysis.

Statistical analysis

To estimate VE we used a generalized linear mixed model (GLMM) for the binary outcomes with a logit link function and "study" modelled as a random effect. Using GLMM the odds ratio (OR), ratio of the odds of vaccination between influenza test-positive cases and influenza test-negative controls, and its 95% confidence interval (95% CI) was calculated. Unadjusted and adjusted VE estimates were calculated by using the formula (1 – unadjusted OR) × 100% and (1-adjusted OR) × 100%, respectively.

To estimate the size of the heterogeneity across datasets, we calculated an intraclass correlation coefficient and its 95% CI based on the Wald test statistic [19,20]. The coefficient can be interpreted as the I^2 measure of inconsistency proposed by Higgins et al., whereby 25% represents small heterogeneity, 50% represents medium heterogeneity, and 75% represents large heterogeneity [21, 22].

The overall VE was estimated separately for a combination of vaccine match (yes/no) and epidemic condition (i.e. non-epidemic seasons (sporadic and local virus activity) and epidemic seasons (regional and widespread outbreaks)). We adjusted the effect sizes for age, gender, interval between symptom onset and swab collection (0-3 days, 4-7 days and > 7 days) , presence of chronic medical condition (yes/no), hemisphere (Northern and Southern), and smoking status. Additionally, we assessed adjusted VE estimates for influenza A(H1N1), A(H1N1)pdm09, A(H3N2) and B separately. Missing data was imputed using multiple imputation with the Predictive Mean Matching (PMM) method assuming the missing-at-random (MAR) mechanism [23]. Participants' missing data were imputed 20 times to reach a relative efficiency of 95% or higher using complete patient and study characteristics as the predictor variables [24].

Finally, we conducted several independent subgroup analyses to estimate VE in different strata. We stratified the analysis based on age categories (i.e. 60-75 years and above 75 years), hemispheres (Northern/Southern), medical conditions for which a sufficient number of patients was available (cardiovascular disease, respiratory disease, and diabetes), and healthy subgroup without any high-risk medical conditions. The reason to solely choose these chronic medical conditions was low power and number of vaccinated cases among elderly with other medical conditions (e.g. cancer, immunodeficiency, etc.). Statistical analyses were done with the GLIMMIX procedure from SAS software (version 9.4).

RESULTS

Description of included studies and datasets

Of all 25 potential data contributors, 17 replied and 9 authors confirmed willingness to participate (Table 1) [1,25-38] and the remainder declined (four potential contributors did not share the data for unknown reasons, two due to the data sharing policy restrictions, and two were not interested in participating in the study). In general the main missing information was from the studies conducted in the North America during influenza seasons 2004-2008 and 2010-2013. Comparing to the

aggregated-data meta-analysis [2], in this study we received 29/53 (55%) potential datasets with 5,210/11,848 (44%) individual participant data. Of 5,210 IPD, 235 (4.5%) had missing information for the laboratory-confirmed influenza outcome, vaccination status and/or patient's unique ID. Ultimately, 4,975 IPD were included in the final analysis (Figure 1).

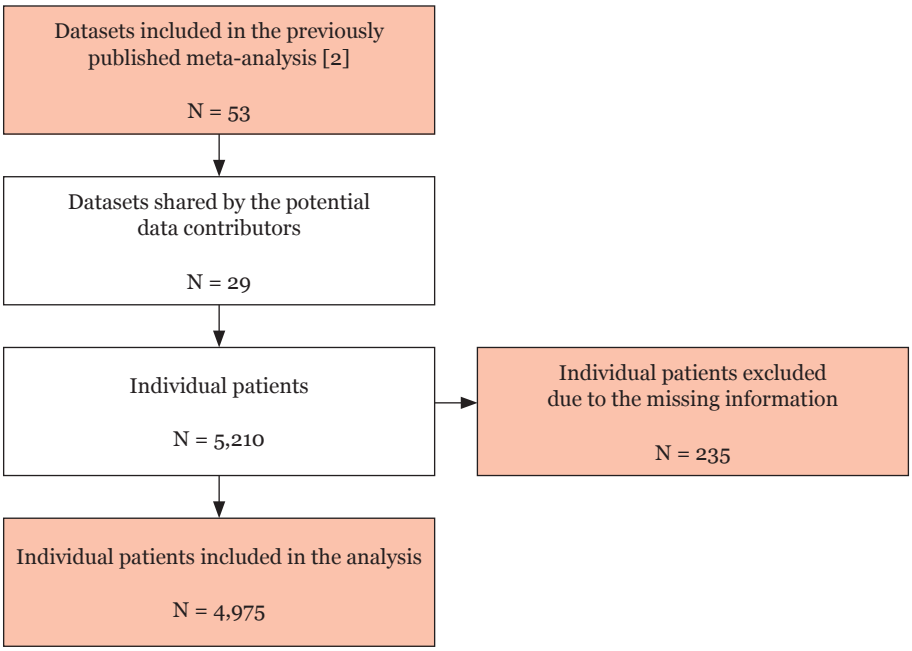

FIGURE 1. Study flow diagram.

TABLE 1. Summary of study characteristics.

First author	Country	Influenza season	Patients Recruitment period	Swab collection period	Outcome	Laboratory test	Case definitions	Vaccination status/vaccine ascertainment	Covariates adjusted for
Castilla and Martinez-Baz et al. [25,26]	Spain	2010-2011	October 2010 to March 2011	Within 4 days of ILI onset	LCI[a] and HLCI[b]	RT-PCR[c]	Patients positive for any influenza virus by RT-PCR	14 days after vaccine administration/Online regional vaccination register	Sex, age group, living in an urban/rural area, calendar period, major chronic conditions, children in the household, pneumococcal vaccination status and calendar period, outpatient visits in the previous year, hospitalization in the previous year
Castilla and Martinez-Baz et al. [2]	Spain	2011-2012	December 2011 to May 2012	< 5 days of ILI onset	LCI and HLCI	RT-PCR	Patients positive for any influenza virus by RT-PCR	14 days after vaccine administration/Online regional vaccination register	Sex, age, major chronic conditions, outpatient visits in the previous year, hospitalization in the previous year, healthcare setting, and period of diagnosis
Castilla and Martinez-Baz et al. [27]	Spain	2012-2013	November 2012 to January 2013	< 5 days of ILI onset	LCI and HLCI	RT-PCR	Patients positive for any influenza virus by RT-PCR	14 days after vaccine administration/Online regional vaccination register	Sex, age, major chronic conditions, health care visit and hospitalization previous year, urban/ rural area, migrant status, children in the household and month

TABLE 1. Summary of study characteristics. (Continued)

Englund et al. [28]	Germany	2010-2011	October 2010 to April 2011	< 7 days of ILI onset	LCI	RT-PCR	Patients who tested positive for influenza A or B using RT-PCR	More than 13 days between vaccination and symptom onset/ Filled form by physicians	Age group, sex, presence of a chronic illness and week of arrival of the specimen at the laboratory
Gefenaite et al. [29]	Lithuania	2012-2013	October 2012 to April 2013	≤ 7 days of ILI onset	LCI	RT-PCR	Patients who tested positive for influenza A or B using RT-PCR	14 days or more between vaccination and symptom onset/ Self-report	Obesity
Kelly et al. [30, 31]	Australia	2007-2014	May to September each year	Within 3 days of ILI onset	LCI	RT-PCR	Patients who tested positive for influenza A or B using RT-PCR	At least 14 days between vaccination and symptom onset/ GP records or patient report	Age and sex (2007-2011), Age, sex and comorbidity (2011-2014)
Lo et al. [32]	Taiwan	2011-2012	July 2011 to June 2012	Only 90% of swabs collected ≤ 7 of ILI onset days	HLCI	RT-PCR and/or viral culture	Patients who tested positive for influenza A/B using RT-PCR and/or viral culture.	If vaccinated before symptom onset/ Physician's report and hospital records	Age, residing regions, underlying medical conditions, intervals between symptom onset and specimen collection
Ntshoe et al. [33]	South Africa	2005-2014	May to September each year	90% within 3 days of ILI onset	LCI	Culture, HAI[d] and/ or PCR	Patients with ILI and positive for influenza A and/ or B	If vaccinated ≥ 2 weeks before symptom onset /Standard data collection forms filled by GPs	Age
McAnerney et al. [34]	South Africa	2010-2013	January 1 2010 to December 31 2013	Within 7 days of ILI onset	LCI	RT-PCR	ILI patients in whom influenza was detected were considered cases	>14 days prior to the onset of illness /Medical records or self-reports	Age, underlying medical conditions and season period where possible
McAnerney et al. [35]	South Africa	2014	May to September 2014	Within 7 days of ILI onset	LCI	RT-PCR and HAI	ILI patients who tested positive for influenza	>14 days prior to the onset of illness / Medical records or self-reports	Age, pre-existing underlying medical conditions and seasonality (first, mid or last third of the season)

TABLE 1. Summary of study characteristics. (Continued)

Suzuki et al. [36]	Japan	2010-2011	December 2010, to April 2011	Less than 5 days of ILI onset	LCI	RIDT[e]	Patients with positive RIDT for influenza A and/ or B	More than 14 days prior to hospital visit /Standardized questionnaire	Age group, chronic conditions, duration of symptom, smoking and alcohol and month of visit
Suzuki et al. [37]	Japan	2011-2012	December 2011 to April 2012	Less than 5 days of ILI onset	LCI	RT-PCR	Patients who tested positive for influenza A or B using RT-PCR	More than 14 days prior to hospital visit/Standardized questionnaire	Age group, underlying conditions, duration from onset to testing and month of visit
Turner et al. [38]	New Zealand	2012	April to February 2012	Within 7 days of SARI onset	HLCI	RT-PCR	Patients with a positive laboratory result for any influenza virus detected by RT-PCR or viral isolation	At least 14 days prior to hospitalization/ Case report form and electronic data extraction from hospital databases	Timing of admission and the estimated propensity for vaccination
Turner et al. [39]	New Zealand	2013	June to November 2013 for SARI cases and May to October 2013 for ILI cases	Within 7 days of ILI or SARI onset	LCI and HLCI	RT-PCR	Patients with a positive laboratory result for any influenza virus detected by RT-PCR or viral isolation	At least 14 days prior to presentation or hospitalization/GP record for ILI cases and self-report for SARI cases	Propensity to be vaccinated and timing admission or presentation during influenza season
Turner et al. [40]	New Zealand	2014	June to August 2014	Within 7 days of ILI or SARI onset	LCI and HLCI	RT-PCR	Patients with a positive laboratory result for any influenza virus detected by RT-PCR or viral isolation	At least 14 days prior to presentation or hospitalization/GP record for ILI cases and self-report for SARI cases	Age and week of admission or presentation in the season

[a]Laboratory-confirmed influenza; [b]Hospitalization due to laboratory confirmed influenza; [c]Reverse transcription polymerase chain reaction; [d]Haemagglutination inhibition test; [e]Rapid diagnostic testing for influenza.

Table 1 (available in the Journal Web Appendix) presents the extent of influenza virus activity, influenza virus (sub)types, vaccine match and the predominant virus(s) circulating during each influenza season, as extracted from the WHO website [14]. In the Northern hemisphere with three influenza seasons (2010/11, 2011/12, 2012/13) two datasets from Spain and Japan measured VE during the 2010-2011 influenza seasons during widespread outbreaks when vaccine strains matched the circulating viruses. Moreover, three datasets from Spain, Japan and Taiwan assessed VE during influenza season 2011-2012. In all three countries widespread outbreaks occurred and vaccine strains did not match the circulating virus subtype A(H3N2) and influenza B. Additionally, one dataset from Spain assessed VE during influenza season 2012-2013 when vaccine strains matched the circulating viruses and virus caused widespread outbreaks. In the Southern hemisphere with ten influenza seasons (2005-2014), eight datasets (2007-2014) were from Australia, three datasets from New Zealand (2012-2014) and ten datasets from South Africa (2005-2014). From the ten influenza seasons in the Southern hemisphere countries, in four seasons influenza vaccine strains matched the circulating viruses or the predominant virus(es) (2005, 2010, 2011, 2013) and in four seasons vaccine did not match (2006 (against A(H3N2), 2007 (against A(H1N1), 2009 (against A(H1N1) and A(H3N2)), 2012 (against A(H3N2) and B)). In the two remaining seasons, 2008 and 2014, the vaccine in Australia matched the predominant virus subtype A(H3N2), while the vaccine in South Africa mismatched the predominant virus subtype A(H1N1) during the influenza season 2008. Additionally, in season 2014 vaccine strains matched the predominant virus subtype A(H1N1)pdm09 in Australia while it mismatched the predominant virus subtype A(H3N2) in South Africa and New Zealand.

Descriptive statistics

Among the 4,975 participants, 3,146 were negative for any type of influenza virus (negative controls (63%)) and 1,829 were positive for laboratory-confirmed influenza virus (cases (37%)). Information about influenza virus (sub)types was available for 1,641 (89%) cases; with 155 (9%) positive cases for influenza A(H1N1), 832 (51%) for A(H3N2), 90 (6%) for A(H1N1)pdm09 and 564 (34%) for influenza

B. Additionally, among cases information on the interval between symptom onset and swab collection was available for 4,237 patients (85%), of which 83% of swabs were collected less than 3 days, 13% between 4 to 7 days and 4% more than 7 days of symptoms onset.

Cases and controls were similar with respect to gender. However, compared with control subjects, cases were slightly older (age > 75 years; 63.7% vs. 60.2%), more among never smokers (53.5% vs. 43.5%), had lower influenza vaccination coverage (28.3% vs. 49.7%), and had a lower incidence of chronic medical condition (92.5% vs. 95.7%). Of the 3,148 patients who had the information on chronic medical conditions, 2,976 patients (94.5%) had at least one chronic medical condition. Cardiovascular disease (n = 1,617), respiratory disease (n = 1,182), and diabetes (n = 1,134) were the main groups for comorbidities for which data was available. For other chronic medical conditions the number of vaccinated cases was limited and therefore estimating VE within these subgroup of patients was not possible (hematologic cancer n = 8; non-hematologic cancer n = 9; rheumatologic diseases n = 1; immunodeficiency n = 6; stroke n = 4; and cirrhosis n = 4). Finally, while cases were more from countries in the Northern hemisphere (62.5% vs. 37.5%), controls were more from Southern hemisphere's countries (57.4% vs. 42.6%) (Table 2).

Influenza VE estimates

In both unadjusted and adjusted models influenza vaccine showed statistically significant effectiveness against laboratory-confirmed influenza during epidemic seasons irrespective of the vaccine match status (matched unadjusted VE: 53.08%; 95% CI 36.86 to 66.61%, mismatched unadjusted VE: 21.74%; 95% CI 5.99 to 34.84%), (matched adjusted VE: 44.38%; 95% CI 22.63 to 60.01%, mismatched adjusted VE: 20.00%; 95% CI 3.46 to 33.68%) (Table 3). Furthermore, the level of heterogeneity across datasets included in the current meta-analysis was low (intraclass correlation coefficient 28.34%, 95% CI 18.22 to 41. 26%).

TABLE 2. Baseline characteristics of laboratory-confirmed influenza cases and test-negative controls.

	Cases (Number/Total (%))	Controls (Number/Total (%))	P-Value*
Gender[a]			0·9175
Male	955/1899 (50·3)	1667/3305 (50·4)	
Female	944/1899 (49·7)	1638/3305 (49·6)	
Age group			0·0116
>75 years	1211/1901 (63·7)	1991/3309 (60·2)	
≤75 years	690/1901 (36·3)	1318/3309 (39·8)	
Smoking[b]			<0·0001
Never	284/531 (53·5)	691/1589 (43·5)	
Former	193/531 (36·3)	744/1589 (46·8)	
Current	54/531 (10·2)	154/1589 (9·7)	
Interval from symptom onset to swab date, days[c]			0·0412
0-3 d	1309/1604 (81·6)	2201/2633 (83·6)	
4-7 d	240/1604 (15·0)	326/2633 (12·4)	
>7 d	55/1604 (3·4)	106/2633 (4·0)	
Chronic condition[d]			0·0002
Yes	1065/1151 (92·5)	1911/1997 (95·7)	
No	86/1151 (7·5)	86/1997 (4·3)	
Seasonal influenza vaccination			<0·0001
Yes	517/1829 (28.3)	1564//3146 (49.7)	
No	1312/1829 (71.7)	1582/3146 (50.3)	
Hemisphere			<0·0001
Northern	1189/1901(62.5)	1409/3309 (42.6)	
Southern	712/1901 (37.5)	1900/3309 (57.4)	

[a] Frequency missing = 6; [b]Frequency missing = 3,092 (59%); [c]Frequency missing = 973 (19%); [d]Frequency missing = 2,062 (40%).

TABLE 3. VE estimates from the mixed-effects model using imputed datasets.

Influenza virus activity	Vaccine match	Vaccine mismatch
	Unadjusted VE% (95% CI) (n = 4,975)	
Non-epidemic	26.15% (-19.15 to 54.23%)	-25.87% (-125.54 to 29.75%)
Epidemic	53.08% (36.86 to 66.61%)*	21.74% (5.99 to 34.84%)*
	Adjusted VE% (95% CI) (n = 4,975)[a]	
Non-epidemic	27.51% (-18.51 to 55.66%)	-4.27% (-89.97 to 42.76%)
Epidemic	44.38% (22.63 to 60.01%)*	20.00% (3.46 to 33.68%)*

VE: influenza vaccine effectiveness; [a] adjusted for age, gender, interval between symptom onset and swab collection, chronic medical condition, and smoking status; * p-value <0.05.

In the subgroup analysis an effect of vaccine match (yes/no) was tested first. There was no significant difference between match and mismatch within the subgroups (adjusted for all potential confounders) (Table 2 Web Appendix). Therefore to increase the power in the subgroup analysis, the estimates were not further stratified by match status.

VE estimates were statistically significant in both Northern (VE: 28.67%; 95% CI 10.55 to 43.12%) and Southern (VE: 24.23%; 95% CI 5.99 to 38.92%) hemispheres, among individuals with cardiovascular disease (VE: 31.48%; 95% CI 6.48 to 49.79%), respiratory disease (VE: 31.18%; 95% CI 2.40 to 51.48%), and elderly aged ≤ 75 years (VE: 32.76%; 95% CI 17.08 to 54.47%) (Table 4). Nevertheless, despite differences in VE estimates, the Wald test statistics did not show any statistically significant difference between different subgroups in each category (Table 2 Web Appendix).

TABLE 4. Subgroup analysis by hemisphere, age and health status.

Subgroup	VE (95% CI)
Adjusted VE in the Northern and Southern hemispheres[a]	
Northern hemisphere	28.67% (10.55 to 43.12%)
Southern hemisphere	24.23% (5.99 to 38.92%)
Adjusted VE among different age categories[b]	
Age ≤ 75	32.76% (17.08 to 45.47%)
Age > 75	16.29% (-8.18 to 55.23%)
Adjusted VE among healthy and high-risk elderly[c]	
Healthy[d]	27.61% (-3.49 to 49.37%)
Cardiovascular disease	31.48%; (6.48 to 49.79%)
Respiratory disease	31.18% (2.40 to 51.48%)
Diabetes	15.57% (-22.21 to 41.67%)

VE: influenza vaccine effectiveness; 95% CI: 95% confidence interval; [a] adjusted for age, gender, interval between symptom onset and swab collection, chronic medical condition, and smoking status; [b] adjusted for gender, interval between symptom onset and swab collection, chronic medical condition, and smoking status; [c] adjusted for age, gender, interval between symptom onset and swab collection, and smoking status; [d] healthy subgroup: subgroup without any chronic medical condition considered in this study.

In the influenza (sub)type analysis, VE estimates were significant for influenza A(H1N1)pdm09 (adjusted VE: 53.19%; 95% CI 10.25 to 75.58%) and A(H3N2) (VE: 21.84%; 95% CI 2.25 to 37.50%), but not for A(H1N1) and influenza B (Table 5).

TABLE 5. VE for influenza (sub)types.

Study	Number of cases/controls per influenza (sub)type			
	A(H1N1)	A(H3N2)	A(H1N1)pdm09	B
Castilla and Martinez-Baz [1,25-27]	62/336	80/335	0/336	0/336
Englund [28]	0/92	0/92	21/92	0/92
Gefenaite [29]	0/18	5/18	4/18	16/18
Kelly [30,31]	1/325	59/325	23/325	0/325
Lo [32]	28/840	353/710	0/849	497/634
Ntshoe and McAnerney [33-35]	10/301	184/301	42/301	42/301
Suzuki [36,37]	0/114	0/114	0/114	0/114
Turner [38-40]	54/1274	151/1274	0/1274	9/1274
Total	155/3300	832/3169	90/3309	564/3094
Adjusted VE* (%) (95% CI)	19.35% (-19.66 to 45.65)	21.84% (2.25 to 37.50%)	53.19% (10.25 to 75.58%)	-1.52% (-39.58 to 26.16%)

VE: influenza vaccine effectiveness; *adjusted for age, gender, interval between symptom onset and swab collection, chronic medical condition, and smoking status.

DISCUSSION

In this study both unadjusted and adjusted overall VE estimates were statistically significant against laboratory-confirmed influenza among inpatients and/or outpatients elderly population during epidemic seasons irrespective of vaccine match status. In general, the effect estimates were stronger when vaccine matched the circulating viruses. Furthermore, in the subgroup analysis by age category and chronic medical condition, although vaccine showed significant effectiveness among individuals with cardiovascular disease, respiratory disease, and those age ≤75 years, we did not find any statistically significant difference between these subgroups and subgroups of healthy, diabetic and elderly age > 75 years in each category. Finally, the overall VE estimates showed substantial variation across influenza (sub)types, with the highest effectiveness for influenza A(H1N1)pdm09 and the lowest for influenza B.

In general, depending on the intensity of the influenza virus activity and antigenic match between the vaccine strains and circulating viruses, influenza vaccine showed slight to moderate protective effect among the elderly population both

in the current meta-analysis and aggregated-data meta-analysis of test-negative design case-control studies [2]. However, compared to the aggregated-data meta-analysis, adjusted VE estimates in this study were somewhat lower (from 36-52% in the aggregated-data meta-analysis to 20-44% in the IPD meta-analysis) during epidemic seasons. Hence, this difference highlights the importance of adjusting for the potential confounders, even in TND as the most efficient observational study design.

Similar to the aggregated-data meta-analysis [2], influenza vaccine seemed to be less effective in the Southern hemisphere compared to the Northern hemisphere in this study, although the Wald test statistics did not show any significant difference between the two hemispheres and confidence intervals overlaps. This VE difference could be due to the different distribution of cases and controls in the Southern hemisphere compared to the Northern hemisphere (more controls in the Southern hemisphere while more cases in the Northern hemisphere). However, this finding needs further investigation. Additionally, in the subgroup analysis, vaccination showed protective benefit in elderly with cardiovascular disease, respiratory disease, and elderly aged ≤75 years. The different VE among the two age categories could partly be explained by decreasing vaccine effectiveness with advancing age due to the age-related immune deficiency known as immunosenescence [3]. However, since we did not find any significant difference between the different age-categories, this result should be interpreted cautiously.

Similar to a recently published meta-analysis assessing VE by type and subtype, in this study VE estimates showed substantial variation across influenza virus(sub) types [4]. However, in our study VE estimates among elderly population were lower than those reported by Belongia et al. [4]. These differences could partly be due to the different studies that were included in these meta-analyses. For instance, in this recently published meta-analysis VE against influenza B among older adults was estimated based on two studies from UK, Canada and a multi-center study by the European network to monitor influenza vaccine effectiveness (I-MOVE) [41-43]. On the other hand, almost 90% of influenza B cases in our meta-analysis belonged to the study conducted by Lo et al. [32] which was not included in the Belongia et al. analysis. Lo et al. study which was conducted in Taiwan during influenza season 2011-2012 when vaccine strain did not match the predominant influenza B virus,

did not find any protection effect for vaccine against influenza B (VE: -66%; 95% CI -132 to -18%) [33]. Therefore, although Belongia et al. found a high VE against influenza B (VE: 63%; 95% CI 33 to 79%) among elderly population, we did not find such an effect against the same influenza type (adjusted VE: -1.52%; 95% CI -39.58 to 26.16%).

This is a first global IPD meta-analysis assessing seasonal influenza vaccine effectiveness among the elderly population over multiple seasons in the Northern and Southern hemisphere countries. For the three influenza seasons 2010-2013 in the Northern hemisphere, the pooled adjusted VE estimates among elderly aged ≥ 60 years within the I-MOVE studies ranged from 59.9% during influenza season 2010-2011 when vaccine strains matched the circulating viruses to 15.1% and 54.1% when vaccine strain did not match the predominant influenza subtype B and A(H3N2) during influenza season 2011-2012 and 2012-2013, respectively [41,44,45].

In this meta-analysis we made exhaustive efforts to collect representative datasets from countries in both Southern and Northern hemispheres. In fact, in most of the included studies, study population was quite representative for the general population of that specific region/country with regard to the general practices and vaccination status (personal communication). Moreover, since the proportion of cases in each influenza season might depend on the influenza virus activity, we estimated overall VE for different geographical spread of virus activity separately [2]. Furthermore, in order to reduce the risk of bias we estimated the adjusted VE by including potential confounders such as the presence of chronic medical condition and taking the effect of vaccine match into account.

In order to interpret the results properly, it is important to note the potential study limitations. First, despite all the efforts to include datasets from all the included studies in the aggregated-data meta-analysis, not all the potential data contributors shared their data. Therefore, part of the difference between the VE estimates presented in this IPD data-analysis and the aggregated data-analysis may have been due to potential selection bias. Furthermore, only three influenza seasons from the Northern hemisphere were included in this meta-analysis, which might limit the generalizability of our findings to this area. Second, we did not receive information on all the requested variables such as influenza vaccination

and number of hospitalizations in previous year. Therefore, we were unable to include other important covariates in the model. Third, for some covariates such as smoking status the missing frequency was substantially high (40% missing frequency). However to compensate for this limitation, data was imputed 20 times to assure the relative efficiency of 95% or higher. Fourth, although in the subgroup analysis influenza vaccine did not show statistically significant effectiveness among the healthy elderly, elderly with diabetes and those aged > 75 years, there was no statistically significant difference between these subgroups in each category (Table 2 Web Appendix). Therefore, conclusions about the VE among different subgroups should be made cautiously. Finally, since in several studies both inpatients and outpatients were enrolled [1,25-27,37,40] and multiple laboratory tests were used [32,33,35], sensitivity analysis could not be conducted to investigate the potential effect of each setting as well as each diagnostic test on VE estimates.

In conclusion, this IPD meta-analysis validates the findings from the previously conducted aggregated-data meta-analysis [2]. In general, in both meta-analyses influenza vaccine showed slight to moderate effectiveness against laboratory-confirmed influenza among elderly population during epidemic seasons irrespective of vaccine match status. Hence, in order to provide a higher protection against influenza and influenza-related complications, influenza vaccines with long-lasting effectiveness among high-risk of elderly population are urgently needed. Additionally, global IPD meta-analysis with universal contributors from more countries are needed to confirm our findings and explore the effect of influenza vaccine among elderly population with high-risk medical conditions.

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APPENDIX

Pre-defined form for the IPD project based on the protocol for case-control studies to measure influenza vaccine effectiveness in the European Union and European Economic Area Member States [18].

Variable name	Type	Values and coding	Definition
Study ID	Numeric	integer	Id allocated to each study by M. Darvishian[1]
Country ID	Numeric	Coded according to international country codes	Identifier uniquely identifying the country
Influenza season (year)	Numeric (continuous)	Unique integer	Influenza season (year) in which IVE[2] has been estimated.
Pat_uni_ID	Numeric (continuous)	Unique integer	Unique patient number that is used in the study.
Pat_bir	Date	dd\mm\yyyy	Date of birth of study participant
Age	Numeric (continuous)	integer	Age of each participants in years
Pat_entry	Date	dd\mm\yyyy	The date that patient has been included into the study.
Case	Numeric (binary)	0 = Control 1 = Case	Laboratory confirmed influenza case or negative control
Sex	Numeric (binary)	0 = female 1 = Male	Sex of study participant
Onset date	Date	dd\mm\yyyy	Date of onset of symptoms
Swab date	Date	dd\mm\yyyy	Swabbing date
Fever	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Malaise	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Myalgia	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Cough	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Sorethroat	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Sudden onset	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Headache	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	
Shortness	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Shortness of breath

Variable name	Type	Values and coding	Definition
Lab results	Numeric (categorical)	0 = Negative 1 = Positive 9 = Do not know	Laboratory results (positive/ negative)
Lab virus	Text		Laboratory results: virus type
Lab_subtype	Text		Laboratory results: virus subtype
Seasonal influenza vaccination	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Vaccinated by the seasonal influenza vaccine
Influenza vaccination date	Date	dd\mm\yyyy	Vaccination (seasonal vaccine) date
Seasvacctype	Text		Type of seasonal vaccine (also brand name)
Panvaccany	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Received pandemic vaccine 2009-10
Vacc_prev1	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Seasonal influenza vaccination in previous year
Vacc_prev2	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Seasonal influenza vaccination two years before
Anemia_spleen	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Enlarged spleen, anaemia
Cirrhosis	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Cirrhosis
Diabetes	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Diabetes and endocrine
Heart_dis	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Heart disease
Hema_cancer	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Hematologic cancer
Immune	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Immunodeficiency and organ transplant
Lungdis	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Lung disease
Nohemcancer	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Nonhematologic cancer
Ren_dis	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Renal disease
Dem_stroke	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Dementia, stroke

Variable name	Type	Values and coding	Definition
Rheumat	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Rheumatologic diseases
Other_dis	Text		Other chronic diseases not mentioned in the list
Severity	Numeric (count)	Integer	Number of hospitalizations previous year for the chronic disease
Fs_bath	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Requires assistance to bathe
Fs_walk	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Requires assistance to walk
Smoking	Numeric (categorical)	0 = Never 1 = Former 2 = Current 9 = Do not know	Never, former (stopped smoking at least 1 year before inclusion in the study, current smoker
Antivir	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Administration of antiviral
Antivirdate	Date	dd\mm\yyyy	Date administration antiviral
Antivirtype	Text		Type of antiviral (also brand name)
Res_home	Numeric (categorical)	0 = No 1 = Yes 9 = Do not know	Exclusion criteria: living in a residential home

1. Study ID will be added later by M. Darvishian.
2. IVE: influenza vaccine effectiveness.

TABLE 1. The extend and type/subtype of reported influenza activity extracted from the WHO website.

First author	Epidemic season	Circulating virus strains	Vaccine strains	Predominant virus	Influenza activity level	Vaccine match	Epidemic condition
Castilla and Martinez -Baz	2010-2011	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H1N1)	Influenza activity occurred early in Western Europe and it reached peaks or declined by January.	Match	Widespread outbreaks
Castilla and Martinez -Baz	2011-2012	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H3N2)	Influenza activity increased in January 2012 with regional and widespread outbreaks reported in Spain.	Mismatch	Widespread outbreaks
Castilla and Martinez -Baz	2012-2013	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011A(H3N2); B/Massachusetts/2/2012-like	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	B	An increased activity was reported in many countries in northern, eastern and central Europe with regional and widespread outbreaks in January.	Match	Widespread outbreak
Englund	2010-2011	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H1N1) and B (mostly Victoria line viruses)	Influenza activity occurred early in Western Europe and it reached peaks or declined by January.	Match	Regional outbreaks
Gefenaite	2012-2013	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011A(H3N2); B/Massachusetts/2/2012-like	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A(H1N1)	An increased activity was reported in many countries in northern, eastern and central Europe with regional and widespread outbreaks in January.	Match	Regional outbreaks
Kelly	2007	A/Solomon Islands/3/2006 (H1N1); A/Brisbane/10/2007 (H3N2); B/Malaysia/2506/2004	A/New Caledonia/20/99(H1N1); A/Wisconsin/67/2005(H3N2); B/Malaysia/2506/2004	A(H1N1) and A(H3N2)	Influenza activity started in June, peaked in July to August and declined in September.	Mismatch	Regional outbreak

TABLE 1. The extend and type/subtype of reported influenza activity extracted from the WHO website. (Continued)

First author	Epidemic season	Circulating virus strains	Vaccine strains	Predominant virus	Influenza activity level	Vaccine match	Epidemic condition
Kelly	2008	A/Brisbane/59/2007 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006	A/Solomon Islands/3/2006 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006	A(H3N2)	Influenza activity started in May and increased in July and August.	Match	Local activity
Kelly	2009	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/Brisbane/59/2007 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006	A(H1N) pdm09	Influenza activity began to increase in June with less extend activity in Australia.	Mismatch	Sporadic activity
Kelly	2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H1N1) pdm09	Pandemic A(H1N1) virus was predominated.	Match	Widespread outbreaks
Kelly	2011	A/California/7/2009 (H1N1)pdm09; A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H3N2)	Influenza activity increased from May and continued by September.	Match	Regional outbreaks
Kelly	2012	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A (H3N2)	In Australia widespread outbreaks were reported in July to August.	Mismatch	Widespread outbreaks
Kelly	2013	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	A/California/7/2009 (H1N1)pdm09 A/Victoria/361/2011 (H3N2) B/Wisconsin/1/2010	A(H1N1) pdm09	Regional to widespread outbreaks were reported in Australia in July and August.	Match	Regional outbreaks
Kelly	2014	A/California/7/2009 (H1N1)pdm09 A/Switzerland/9715293/2013 (H3N2) B/Phuket/3073/2013	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	A(H1N1) pdm09	Influenza activity in Australia increased from May and caused widespread outbreaks in August and September.	Match	Widespread outbreaks
Lo	2011-2012	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	B	Sporadic and localized influenza B activity reported by a number of countries in Asia.	Mismatch	Widespread outbreaks

TABLE 1. The extend and type/subtype of reported influenza activity extracted from the WHO website. (Continued)

First author	Epidemic season	Circulating virus strains	Vaccine strains	Predominant virus	Influenza activity level	Vaccine match	Epidemic condition
Ntshoe	2005	A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Hong Kong/333/01	A/New Caledonia/20/99(H1N1); A/Wellington/1/2004(H3N2); B/Shanghai/361/2002	A(H1N1)	Influenza activity began in April and increased during May.	Match	Regional outbreaks
Ntshoe	2006	A/New Caledonia/20/99(H1N1); A/Wisconsin/67/2005(H3N2); B/Malaysia/2506/2004	A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Malaysia/2506/2004	A(H3N2)	Influenza activity began in April with outbreaks reported in South Africa.	Mismatch	Regional outbreaks
Ntshoe	2007	A/Solomon Islands/3/2006 (H1N1); A/Brisbane/10/2007 (H3N2); B/Malaysia/2506/2004	A/New Caledonia/20/99(H1N1); A/Wisconsin/67/2005(H3N2); B/Malaysia/2506/2004	A(H3N2)	Influenza activity started in June, peaked in July to August and declined in September.	Mismatch	Regional outbreaks
Ntshoe	2008	A/Brisbane/59/2007 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006	A/Solomon Islands/3/2006 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006	A(H1N1)	Influenza activity started in May and increased in July.	Mismatch	Regional outbreaks
Ntshoe	2009	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/Brisbane/59/2007 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006	A(H1N1) and A(H3N2)	Influenza activity began to increase in April with widespread outbreaks in South Africa in June.	Mismatch	Widespread outbreaks
McAnerney	2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H3N2) and B	Activity increased from July and had declined in most countries by September	Match	Local activity
McAnerney	2011	A/California/7/2009 (H1N1)pdm09; A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H1N1) pdm09	Activity increased from May and declined in August.	Match	Regional outbreaks

TABLE 1. The extend and type/subtype of reported influenza activity extracted from the WHO website. (Continued)

First author	Epidemic season	Circulating virus strains	Vaccine strains	Predominant virus	Influenza activity level	Vaccine match	Epidemic condition
McAnerney	2012	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H3N2) and B	In South Africa, influenza B activity increased from July to become regional in August. Moreover, A(H3N2) regional outbreaks reported in August.	Mismatch	Regional outbreaks
McAnerney	2013	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	A/California/7/2009 (H1N1)pdm09 A/Victoria/361/2011 (H3N2) B/Wisconsin/1/2010	A(H1N1) pdm09	Regional and widespread outbreaks occurred from June until August in South Africa.	Match	Widespread outbreaks
McAnerney	2014	A/California/7/2009 (H1N1)pdm09 A/Switzerland/9715293/2013 (H3N2) B/Phuket/3073/2013	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	A(H3N2)	local and regional outbreaks were reported in July and August in South Africa.	Mismatch	Regional outbreaks
Suzuki	2010-2011	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H1N1)	Influenza activity started in September and continues to increase by January.	Match	Widespread outbreaks
Suzuki	2011-2012	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H3N2)	Influenza activity started in September with widespread activity in January 2012.	Mismatch	Widespread outbreaks
Turner	2012	A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); B/Wisconsin/1/2010	A/California/7/2009 (H1N1)pdm09; A/Perth/16/2009 (H3N2); B/Brisbane/60/2008	A(H3N2)	Influenza activity started in May and continued to increase with widespread activity in August.	Mismatch	Widespread outbreaks
Turner	2013	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	A/California/7/2009 (H1N1)pdm09 A/Victoria/361/2011 (H3N2) B/Wisconsin/1/2010	A(H1N1) pdm09 and A(H3N2)	Sporadic to local activity was reported in New Zealand from May through August.	Match	Local activity
Turner	2014	A/California/7/2009 (H1N1)pdm09 A/Switzerland/9715293/2013 (H3N2) B/Phuket/3073/2013	A/California/7/2009 (H1N1)pdm09 A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012	A(H3N2) and A(H1N1) pdm09	New Zealand had regional outbreaks in September.	Mismatch	Regional outbreaks

TABLE 2. Wald test statistics for the subgroup analysis.

Subgroup		p-value
Differences between match and mismatch within subgroups	Healthy	0.95
	Cardioavascular disease	0.23
	Respiratory disease	0.35
	Diabetes	0.71
	Northern hemisphere	0.45
	Southern hemisphere	0.10
	Age ≤ 75	0.25
	Age > 75	0.15
Differences between different subgroups in each category	Healthy vs. Cardiovascular	0.64
	Healthy vs. Respiratory	0.68
	Healthy vs. Diabetes	0.54
	Age ≤ 75 vs. Age > 75	0.44
	Northern Vs. Southern hemispheres	0.70